Multimodal MRI markers of nigrostriatal pathology in Parkinson's disease

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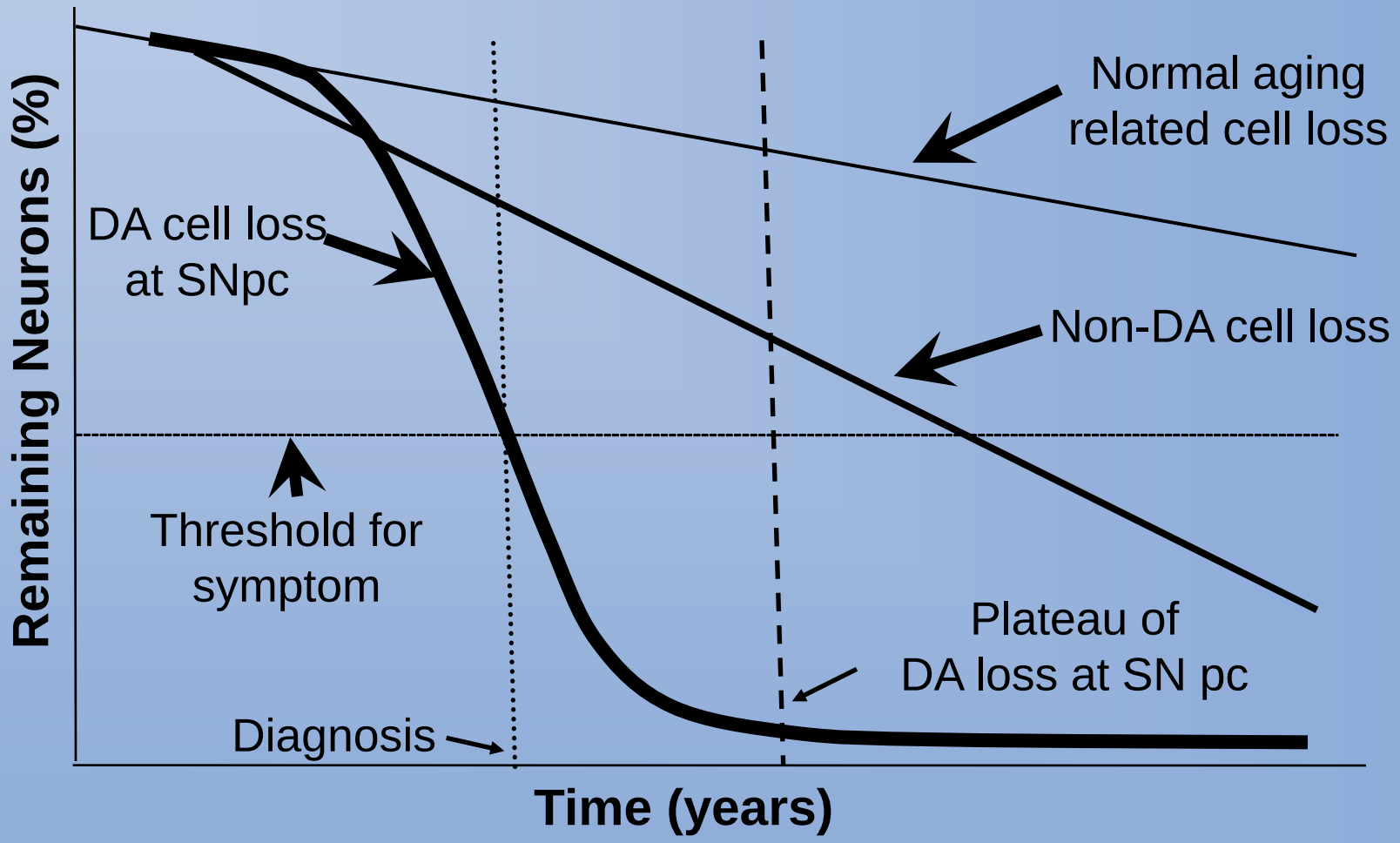
Parkinson's disease

- First described in 1817 by James Parkinson as "Shaking Palsy."
- Cardinal Signs
  - Resting tremor
  - Bradykinesia-slowness
  - Rigidity-stiffness
  - Postural/Gait disorder

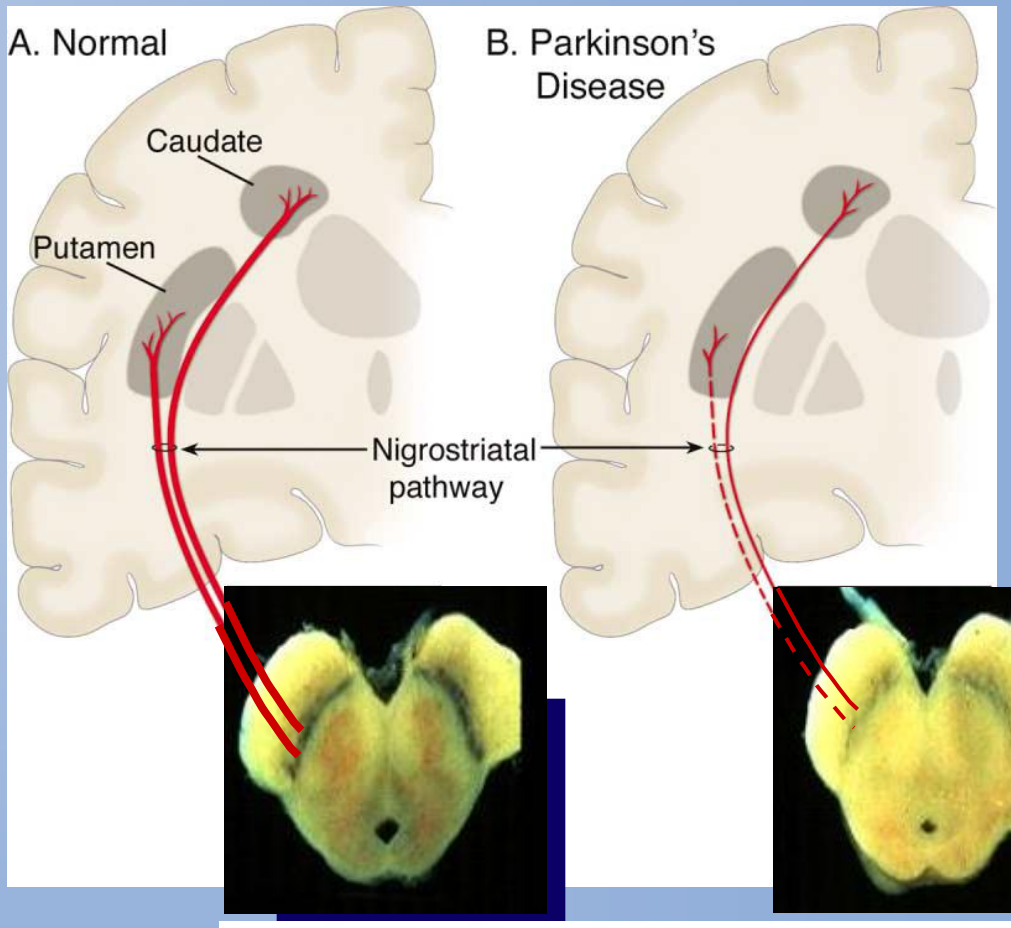
New definition of Parkinson's disease and concepts of its progression (Lang 2007)



Modified from Lang 2007, The progression of Parkinson disease: a hypothesis

Basic Pathology of PD

* *Nigrostriatal changes



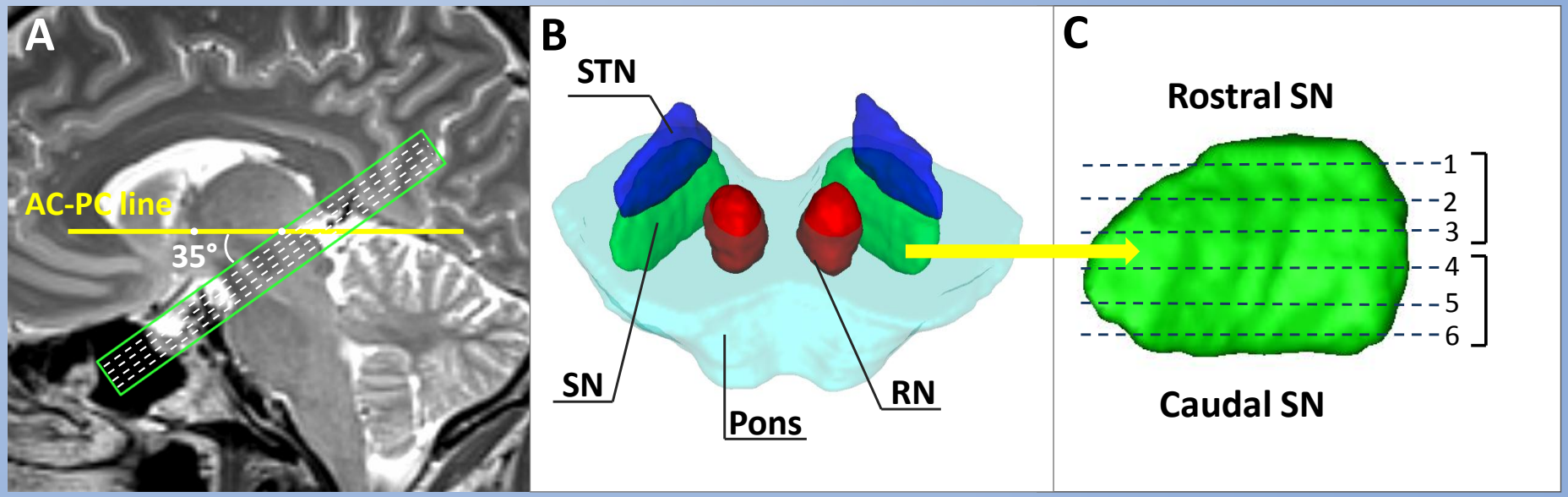
Modified from Dauer & Przedborski, Neuron, 2003

Histopathological changes in Substantia nigra of PD brain

- Dopaminergic neuronal cell loss
- Presence of Lewy bodies or Lewy neurites
- Greater fibrillary astrocytosis.
- Inflammatory cell infiltration.
- Extraneuronal neuromelanin.

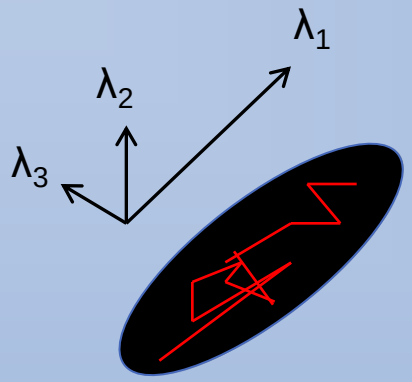
- Iron overload
  - First described in the 1988 (Reiderer et al.)
  - In most severe, but not milder, cases

Beauty of MRI in biomarker research:



- We can dissect brain in living person without using a scalpel
- We can capture spatial changes in nigrostriatal system in PD!
- We can detect cellular, chemical infrastructure changes in PD!
- We can delineate the temporal changes associated with PD progression!

Diffuse Tensor Imaging (DTI)



$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \langle\lambda\rangle)^2 + (\lambda_2 - \langle\lambda\rangle)^2 + (\lambda_3 - \langle\lambda\rangle)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

- Measure the diffusivity of water molecules.
- More limited in the direction of diffusion
  - high Fractional Anisotropy (FA) value
- Traditionally used to study white matter
  - Basser 1996;
- Recently also used to study gray matter
  - Mori and Zhang 2006

DTI to measure SN changes in PD

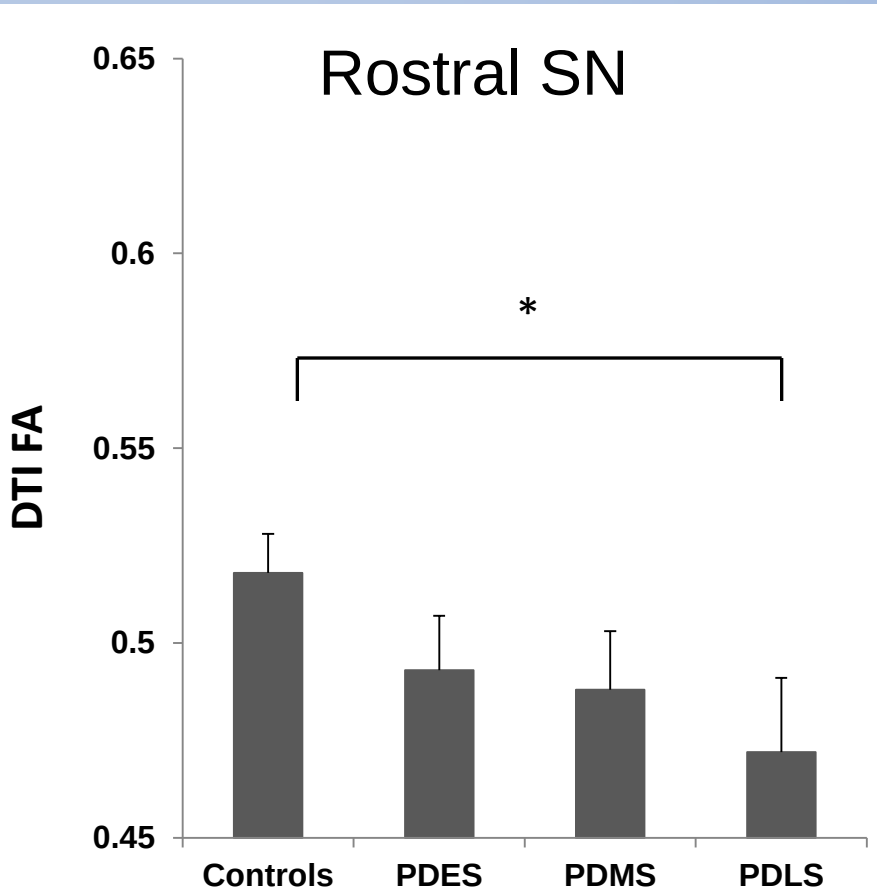
- In a MTPT-treated murine model, DTI measures were significantly correlated with the number of SN DA neurons lost
  - Bosca 2007
- In humans, decreased FA measures in the SN of PD patients have been reported.
  - Chan 2007, Vaillancourt 2009, Peran 2010, Du 2011

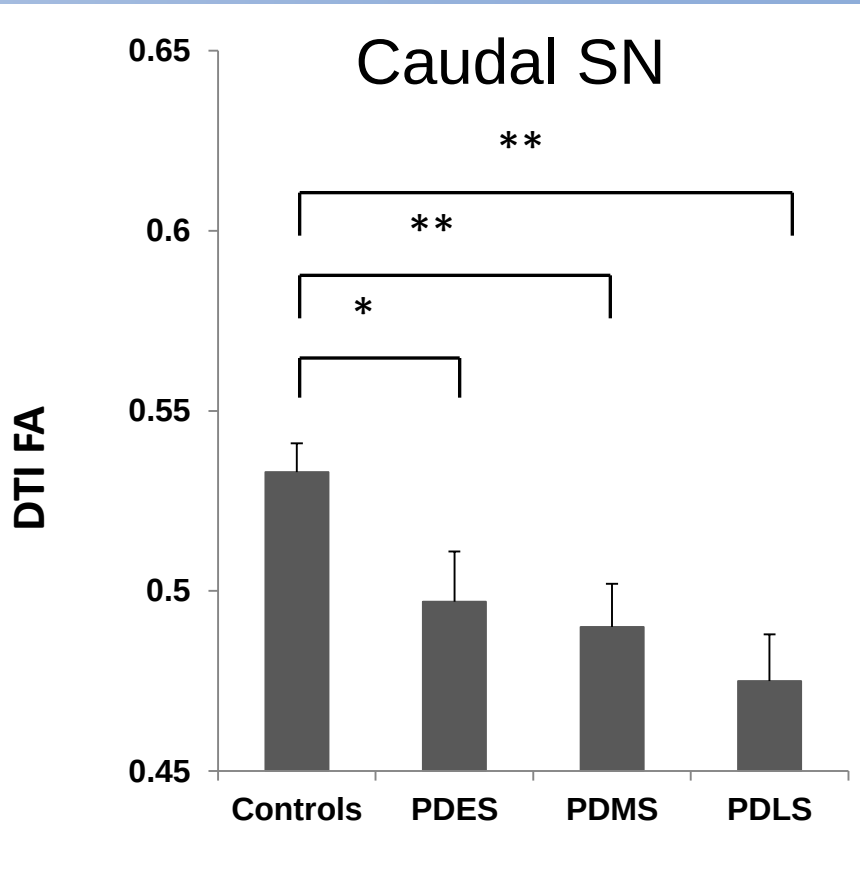
Pilot study

	Controls	PD total	PDES < 1 yr	PDMS 1-5 yrs	PDLS > 5yr
Sex-M/F	13/15	23/17	7/8	8/6	8/3
Age-yrs	60 (7)	61 (8)	60 (10)	59 (6)	63 (8)
HY-I/II/III	NA	13/22/4	8/5/1	4/9/1	1/8/2
Duration-yrs	NA	4.2 (4.7)	0.5 (0.5)	3.3 (1.1)	10.4 (4.3)
LEDD-mg/d	NA	528(400)	277(224)	456(199)	960(444)
UPDRS III	NA	23(15)	17(9)	22(11)	35(20)

Du et al, 2012

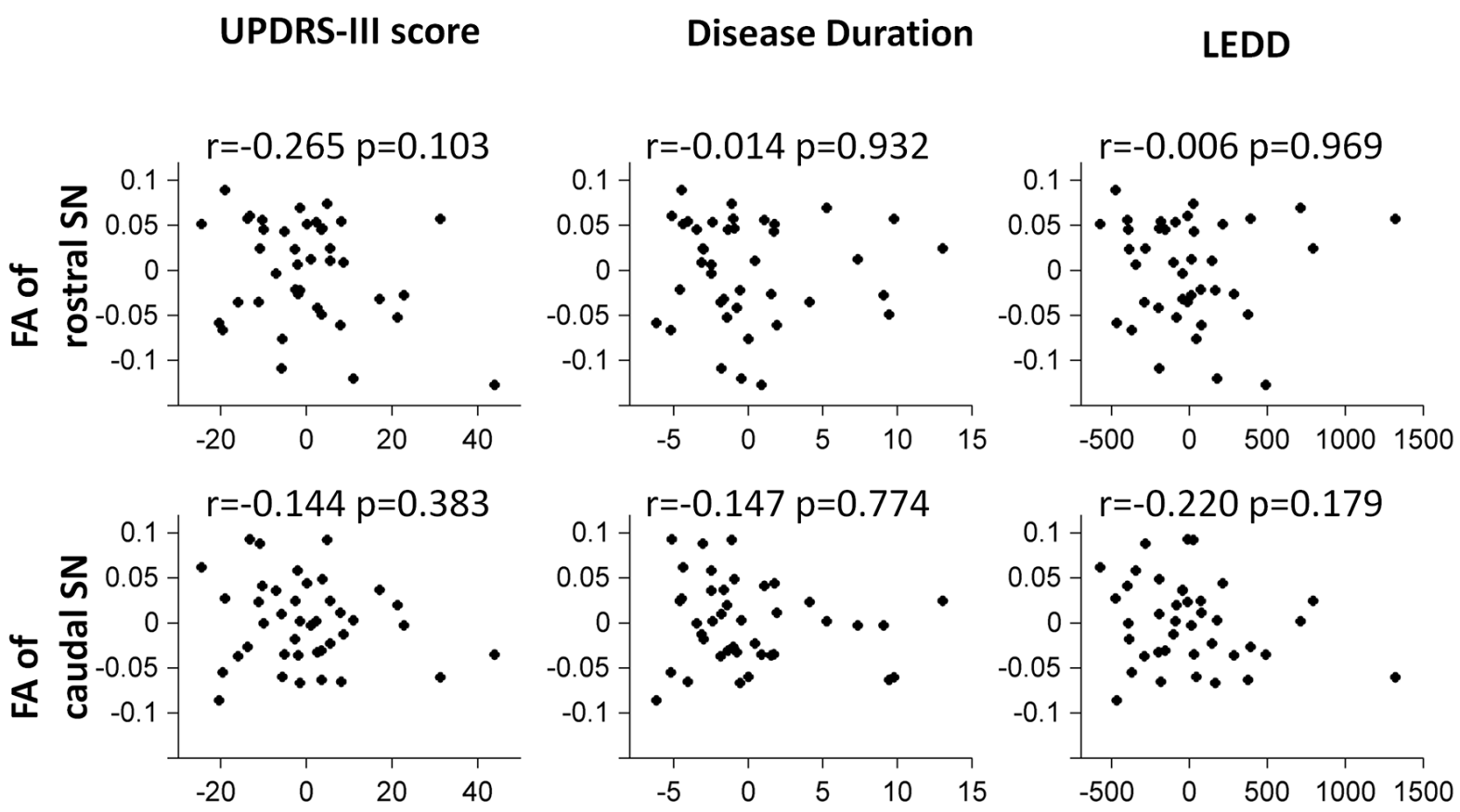
FA changes in SN follow the spatial and temporal pattern of cell loss in the SN





Du et al. 2012

Lack of clinical correlation of FA data



Du et al, 2012

What might be responsible for the DTI changes in SN of PD brain?

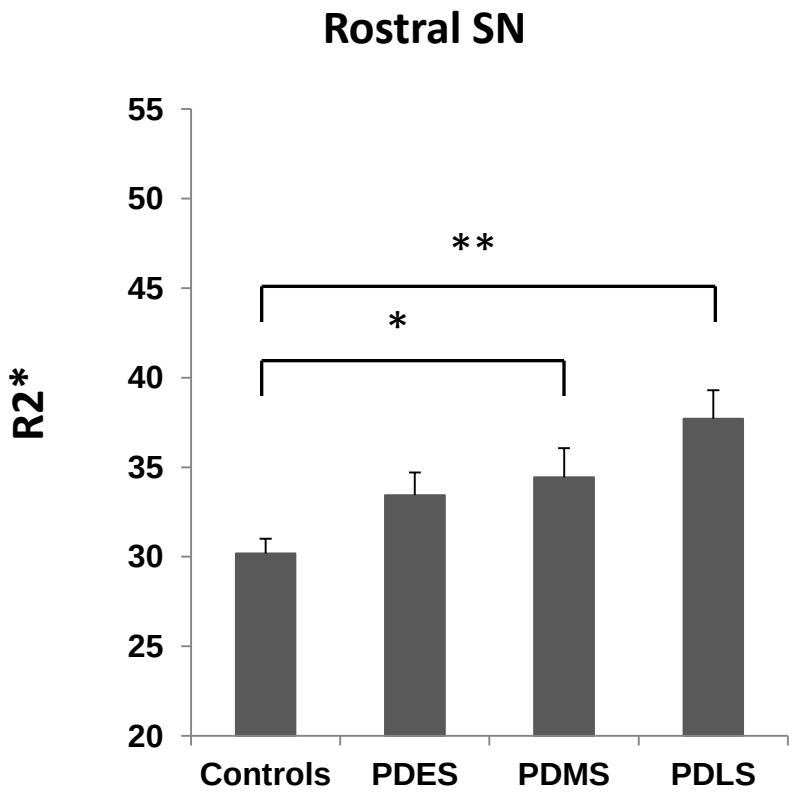
- Dopaminergic neuronal cell loss
- Presence of Lewy body, or Lewy Neurites
- Greater fibrillary astrocytosis.
- Inflammatory cell infiltration.
- Extraneuronal neuromelanin.
- Iron accumulation

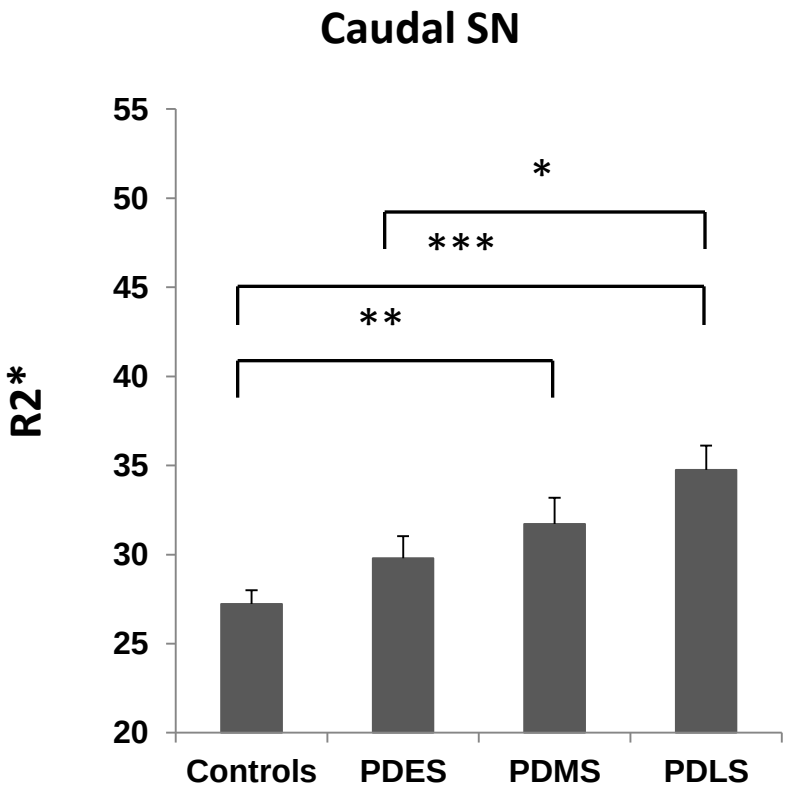
- *All possible except iron*
  - *but need pathological correlation of MRI data*

The transverse relaxation rate (R2*) to measure SN changes in PD

- R2* was correlated with Fe content *in vivo.*
  - Graham et al., 2000; Martin, 2008; Langkammer 2010
- R2* measures have been shown to be increased in the SN of PD patients
  - Graham 2000; Martin 2008, Peran 2010, Du 2011
- Some reports that SN R2* correlated selectively with certain aspects of clinical measurements
  - Martin 2008, Peran 2010

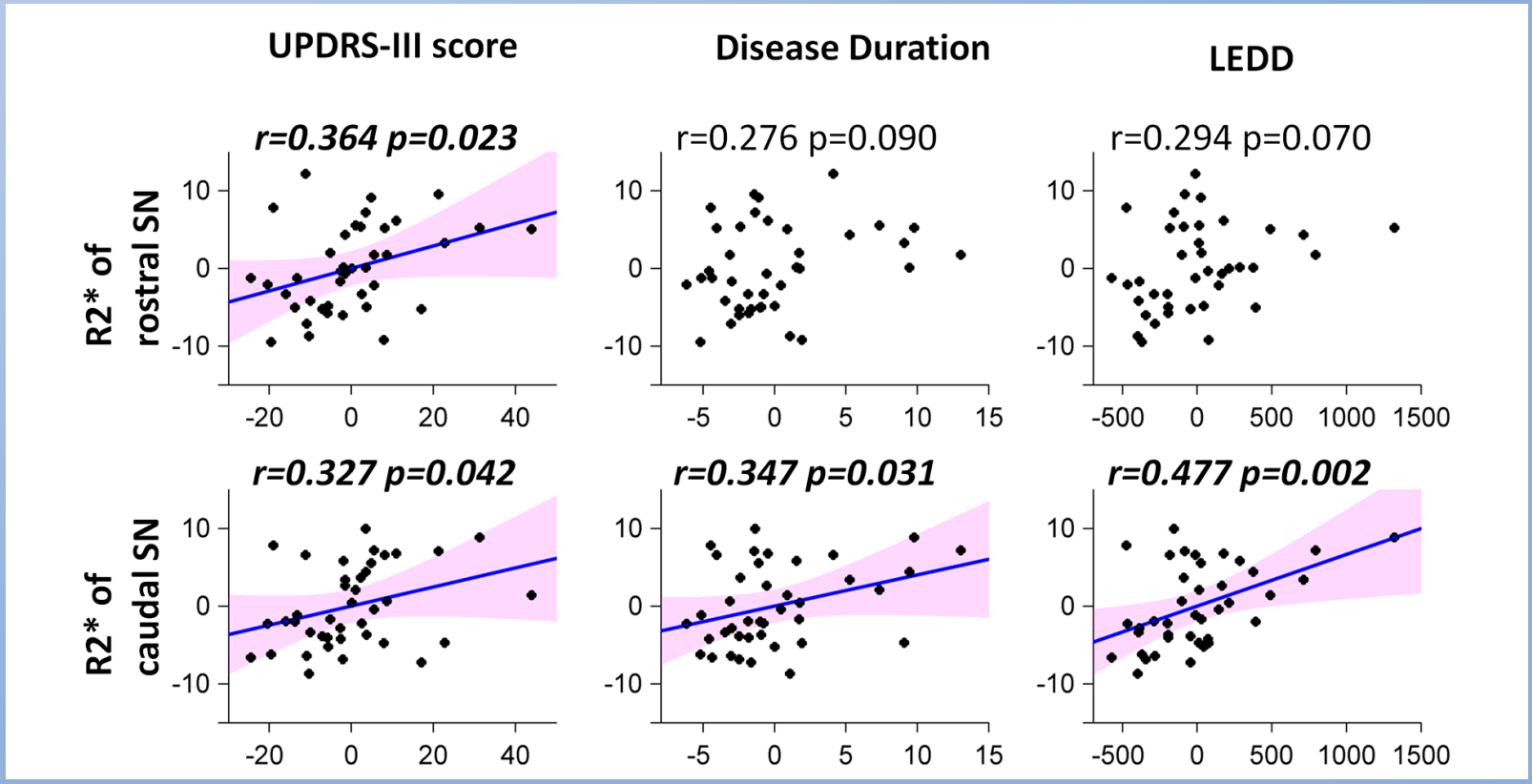
R2* may provide a valid Fe marker in the SN for PD progression





Du et al, 2012

Clinical correlations



Du et al, 2012

Aim 1: Establish the differential roles of FA and R2* in PD detection and progression

- Hypothesis: FA and R2* measures reflect different aspects of nigrostriatal pathology that can be used as biomarkers for diagnosing PD and following its progression
  - FA (DTI) may mark the PD-related pathological changes in the SN
  - R2* may provide a valid Fe marker in the SN for PD progression

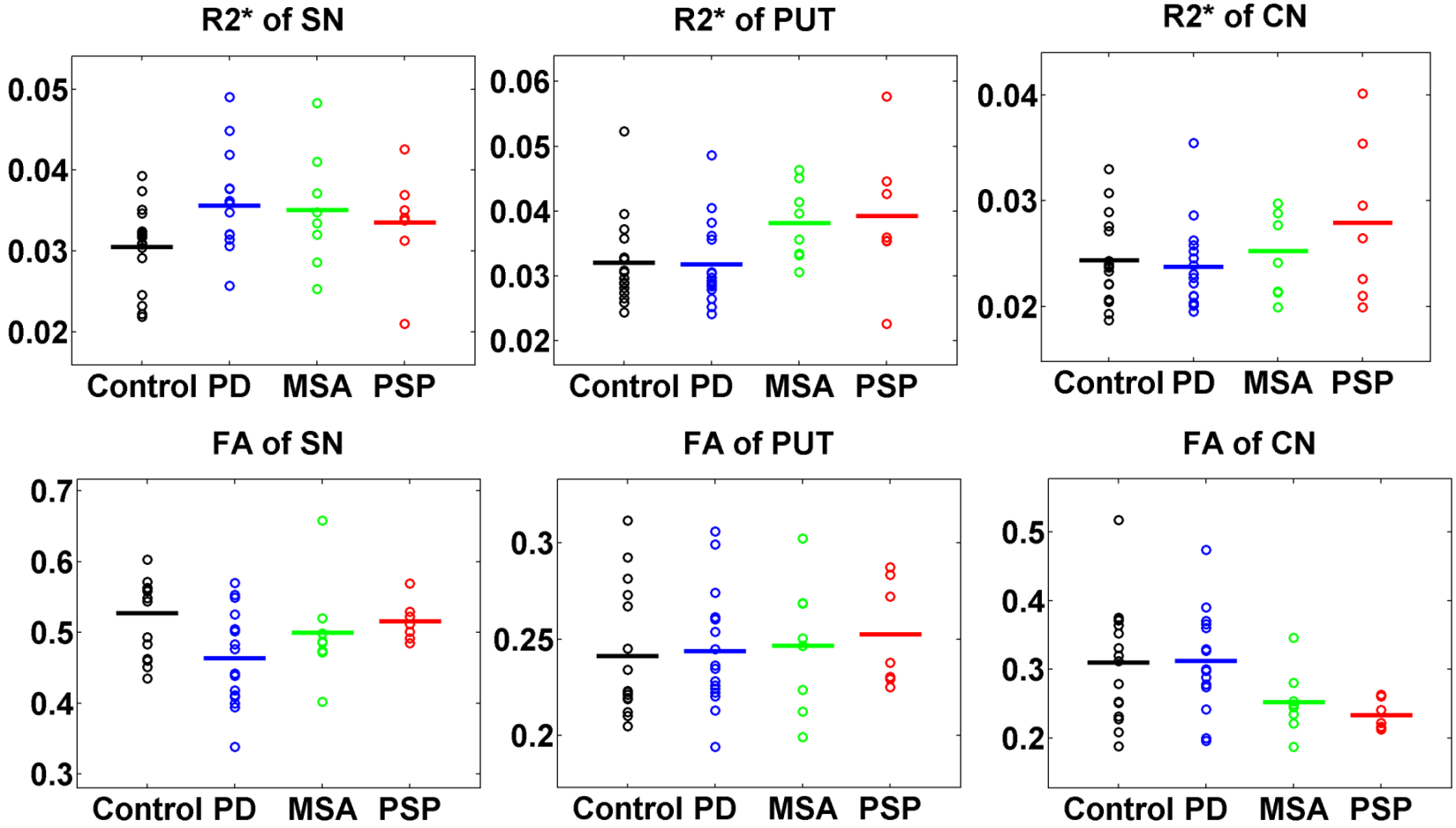
- Approach
  - 87 PD
    - 27 PD subjects<1 yr,
    - 20 PD subjects with 1-5 yrs,
    - 20 PD subjects with 5-10 yrs,
    - 20 PD subjects >10 yrs
  - 58 Controls
  - Brain MRI at baseline, 18 m, and 36 m
  - Clinical measurement at every 6 m

Can combine FA and R2* differentiate PD from PDism?

	Controls	PD	PSP	MSA
N	16	16	7	8
Age	60 (8)	59 (9)	78 (13)	75 (7)
Sex (F/M)	7/9	8/8	0/7	2/6

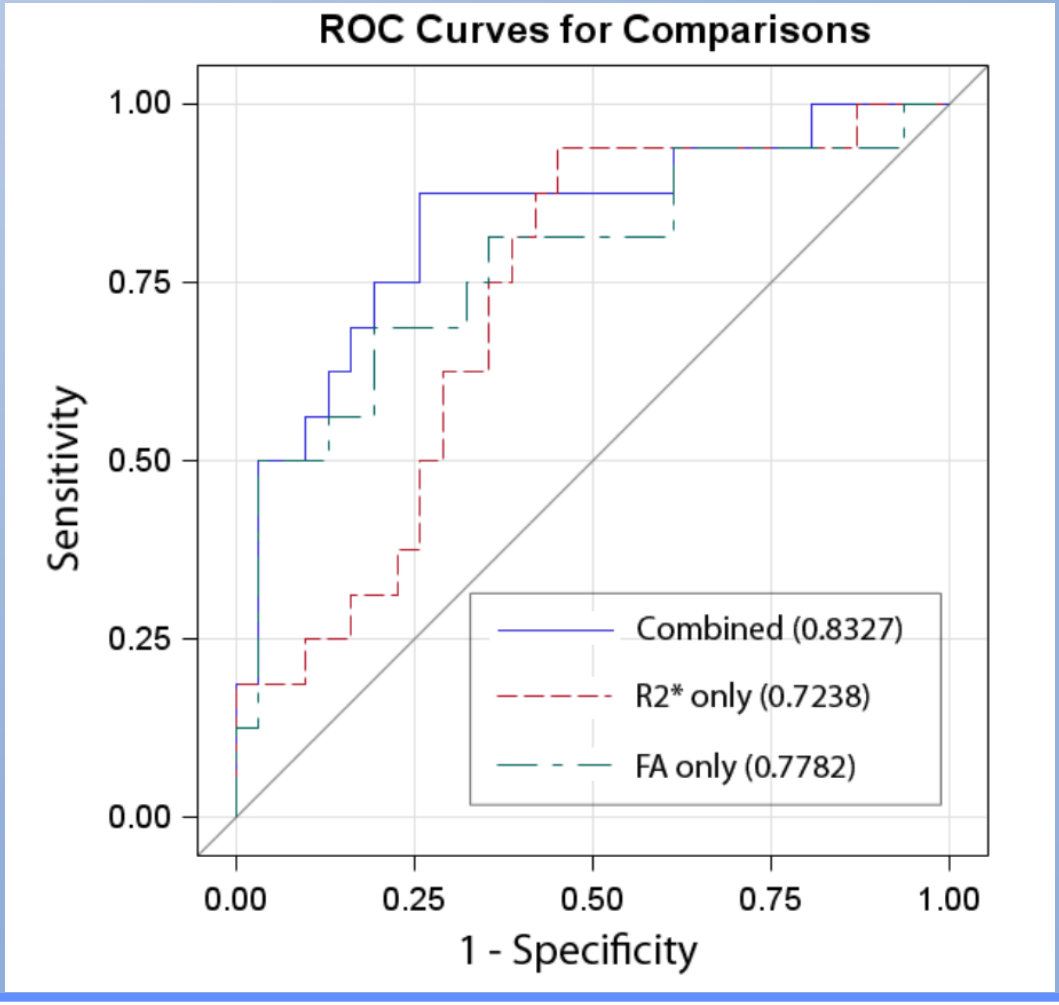
Huang's group unpublished data

There is different pattern of FA and R2* in nigrostriatal structures in PDism



Huang's group unpublished data

Combined FA and R2* enhance discrimination



Huang's group unpublished data

Aim 2:Demonstrate that nigrostriatal DTI & R2* differentiate PD from PDism

- Hypothesis: Combined DTI and R2* measurement may can capture these differential patterns of nigrostriatal injury and provide discrimination between PD and PDism.

- *Approach*
  - 20 PSP
  - 20 MSA
  - Brain MRI , clinical assessment will be obtained at baseline
  - Sensitivity and specificity of individual and combined MRI measures in diagnosing PD will be estimated.

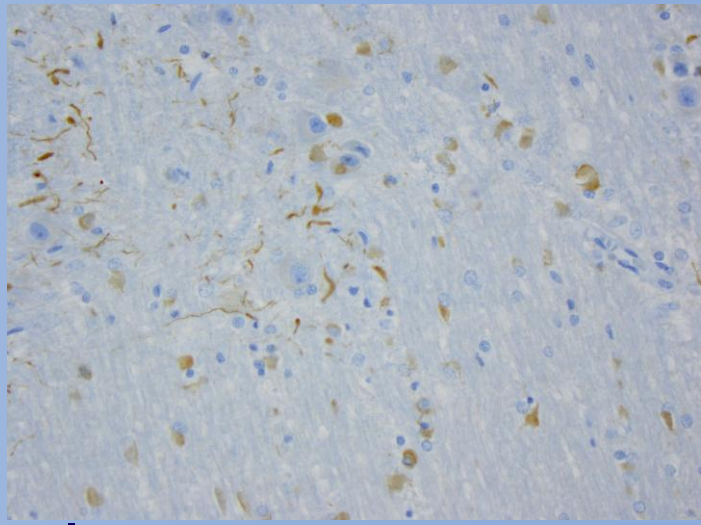
Aim 3. Interrogate Fe-related proteins in body fluids as biomarkers of PD

- *Hypothesis*: Fe-related proteins will have a unique profile in PD that can be used as a biomarker to inform about disease onset and its progression.

- *Approach*
  - Obtain body fluid from all willing subjects
    - Blood
    - Urine
    - CSF
  - Obtain Fe-related proteins such as hepcidin, ferritin and transferrrin in the above body fluid
  - Interrogate their relationships to clinical and MRI measures (in Aims 1 and 2).

Aim 4. Obtain MRI and postmortem pathological correlation data

- Obtain postmortem brain



- Perform postmortem diagnoses
  - α-synuclein, amyloid (Aβ), tau, ubiquitin
- Obtain following tests in nigrostriatal structures and correlate these levels with MRI measures.
  - Tyrosine hydroxylase positive neurons-(DA neuronal markers)
  - Myelin and glial derived growth factors (glial cell markers)
  - Fe staining, ferritin, hepcidin (iron markers)

Acknowledgements

- My patients and their families
- Many volunteers and their families
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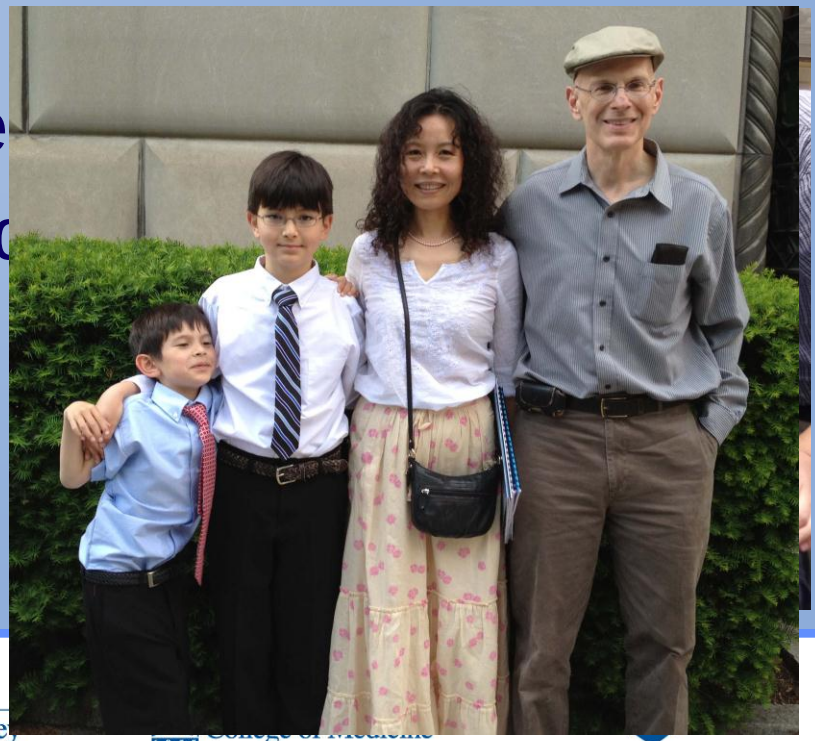
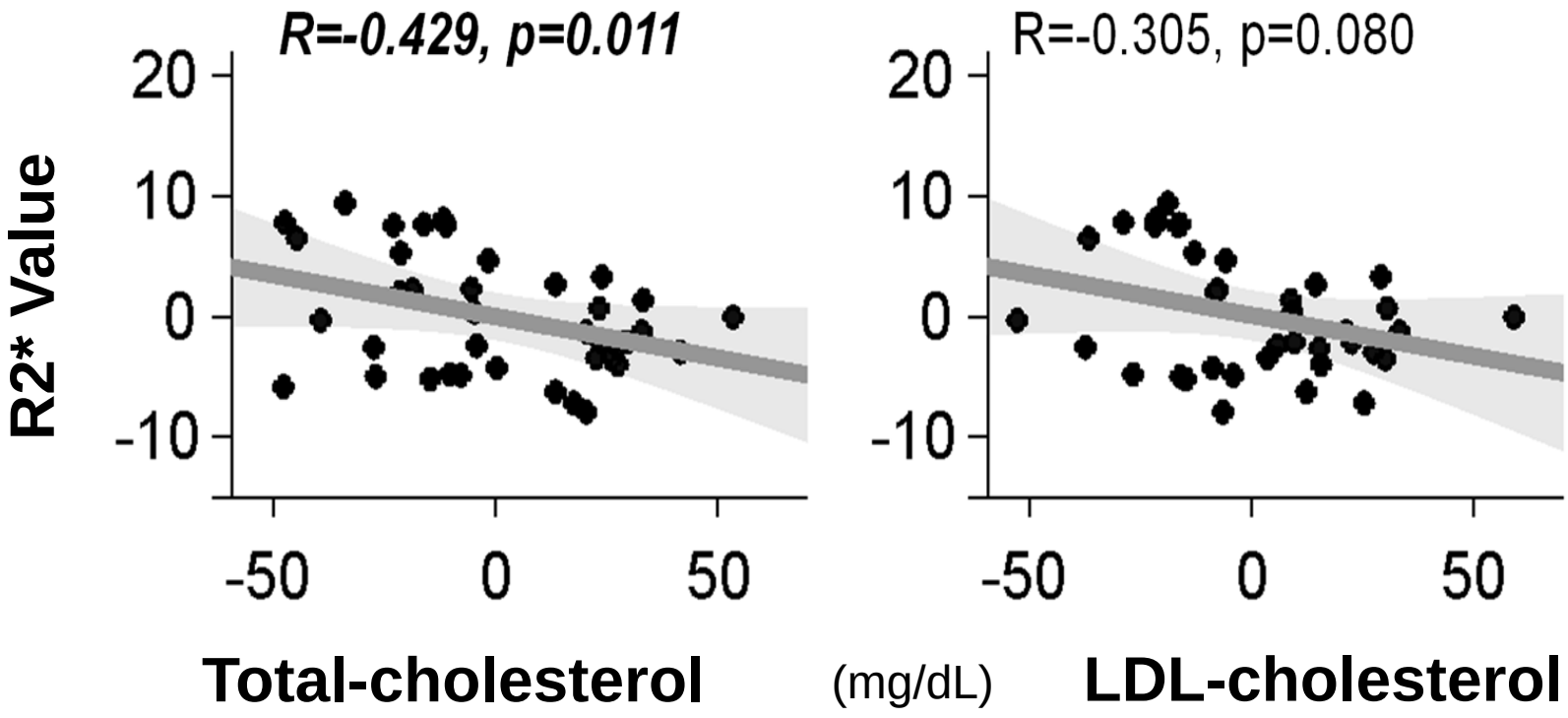
  - NIA (K23, 2003-2008); NINDS (R01, 2009-2014), NIEHS (R01, 2011-2015)
- Pennsylvania Tobacco Se
- Personal gifts from many c program.
- *.. and of course*



Higher cholesterol associated with lower iron (R2* values) in SN



Du et al. PlosOne 2012